Multi-Scaled Stochastic Simulation of Cell-to-Cell Signaling

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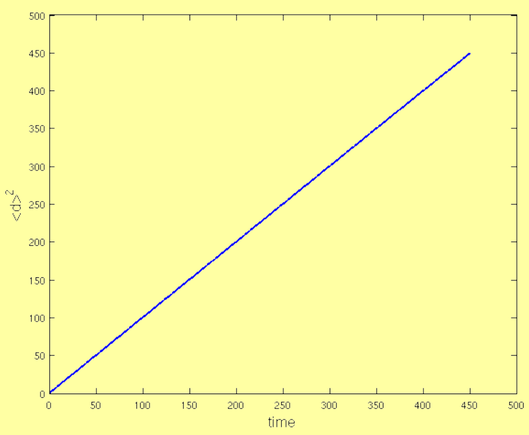
Abstract: A multi-compartment, multi-scale, agent-based simulation was developed, describing the interaction between cells in a medium. The simulation follows the stochastic processes that occur within each cell, while allowing the cells to interact with the extra-cellular medium through secretion of molecules and binding of cell-surface receptors, thus enabling cell-to-cell signaling. The extra-cellular medium is modeled by a square two-dimensional lattice, in which the cells are randomly distributed so that some lattice squares contain a single cell while other squares are vacant. Secreted molecules diffuse through the lattice using a stochastic Monte-Carlo algorithm where each molecule can move to a neighboring matrix square at each time step with a certain probability. This approach ensures that the molecules display a random walk behavior at low concentrations, while maintaining the required diffusion behavior at higher concentrations. To address the problem that the extra-cellular and intra-cellular mediums have different time scales, a modification to the Gillespie algorithm was developed. In the modified Gillespie algorithm each cell is simulated as an independent agent for a pre-defined time interval, followed by a synchronization with its local extra-cellular medium. As an example for the usability of the algorithm we simulated the response of Human dendritic cells (DCs) when infected by a virus (NDV). Infected DCs secrete interferon molecules that diffuse in the extra-cellular medium and bind to other cells. The DCs in the simulation are modeled by the number of bound interferon cell-surface receptors, and the products of the *IFNB1* and *DDX58* genes.

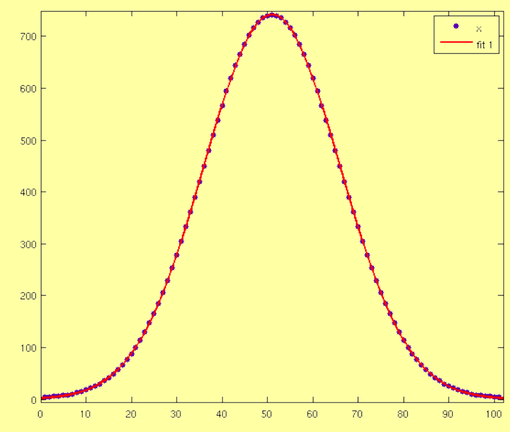
Monte-Carlo Simulation of Diffusion

Requirements:
- Diffusion for both high and low concentrations
- Allow stochastic analysis

Solution:
- At each time-step, allow half the molecules to pass to a neighboring cell
- For each diffusing molecule, choose direction randomly
- Low concentrations – random walk
- High concentration – diffusion
- Diffusion allows choosing the correct time step



Low concentrations produce random walkers with average displacement that increases like the square root of time

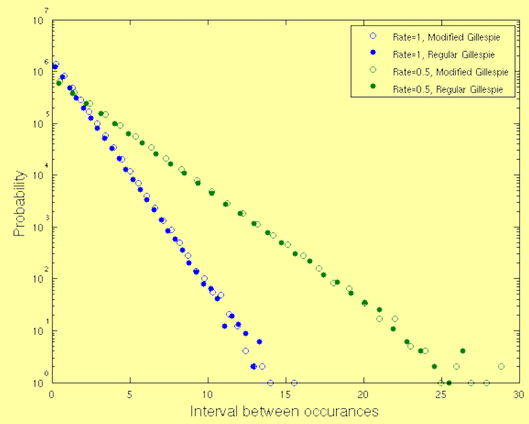


High concentrations produces a Gaussian distribution that evolves in time similarly to a solution to the diffusion equation

Modified Gillespie Simulation of Single Cells

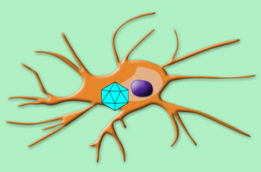
Problems with regular Gillespie simulation:
- Extra-cellular conditions are not constant.
- Extra-cellular simulation time-steps are constant, while internal time-steps are variable

Solution:
- If a Gillespie time-step overshoots an external update, only adjust the time to the update time, then continue Gillespie simulation with new cell conditions
- Retains Markovian assumption with correct statistics



Using the modified Gillespie simulation with two processes without changing external conditions, both processes display the same exponential distribution as a regular Gillespie simulation.

Comparing Simulation with Experimental Results



NDV-infected DC

IFNB1 production and interferon secretion in infected cells

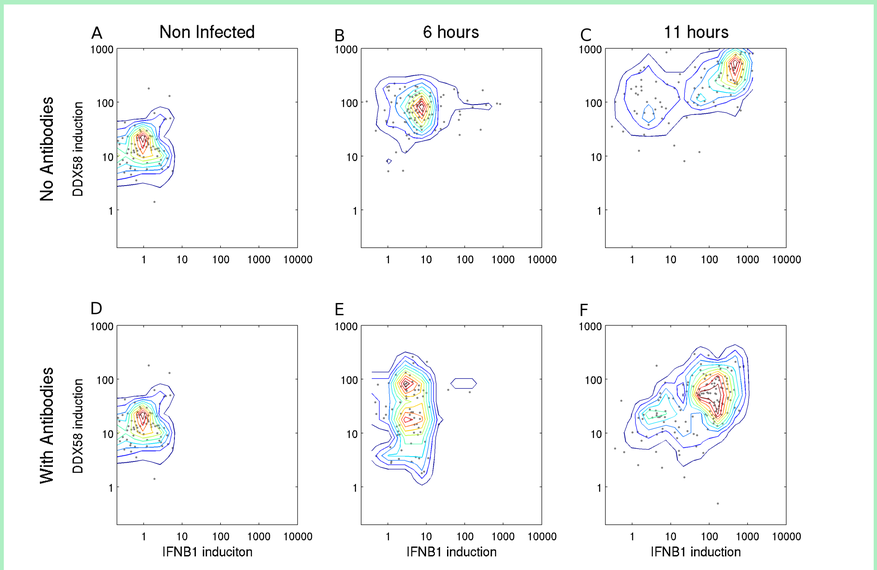
DDX58 induction and RIG-I production in all cells (protecting from infection?)

Single cell PCR measurements of DDX58 and IFNB1 (A-C) show that even at the single cell level DDX58 increases earlier than IFNB1.

A possible explanation can be that only a small percentage of the cells produce IFNB1, and they induce the others (early responders hypothesis). Another hypothesis is that all the cells produce extremely low levels of IFNB1 that are hard to separate from noise (population response hypothesis).

The early responder hypothesis is hard to test experimentally, since we get only about 100 cells per experiment. The population response hypothesis is hard to test experimentally, since IFNB1 levels are close to noise levels.

Introducing antibodies to block interferon signaling (D-F) block DDX58 induction in non-infected cells. However, all infected cells eventually get activated.



Simulation results mimic the experimental results, both on average (A) and at the single cell level (B,C). The simulation showed that early responder cells facilitate the activation of infected cells.

Using the simulation we see that the noisy DDX58 basal activity can explain the difference in response between different cells.